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Chemoselective Conversion of α-Unbranched Aldehyde to Amide, Ester, and Carboxylic Acid by NHC-Catalysis

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Depending on the N-heterocyclic carbene catalyst utilized, α-unbranched aldehyde selectively provided amide, ester, or carboxylic acid through oxidation by NCS. The α-unbranched aldehyde underwent these reactions chemoselectively in the presence of an aromatic or α-branched aldehyde.

N-Heterocyclic carbenes (NHCs) are used as organocatalysts for various transformations.[1] NHC-catalyzed esterification and amidation of α-oxidized aldehydes were demonstrated[2] using α,β-epoxyaldehyde,[2a,f] α-haloaldehyde,[2b,f,g] alkenal,[2c,f,g] and α-acyloxyaldehydes[2k] as substrates. Direct conversion of aldehydes to esters or amides was also achieved by NHC-catalysis,[3] but only aromatic and unsaturated aldehydes were suitable for the reported direct amidation. Herein, we report a new method for direct conversion of α-unbranched aldehydes to amides, as well as ester and carboxylic acid, with NHC-catalysis. The first report of an NHC-dependent selectivity switch of nucleophiles is also described.

We unexpectedly found that diethylamide **3a** was produced in 18% yield when hydrocinnamaldehyde (**1a**) and triethylamine were heated in refluxing toluene in the presence of benzoyl peroxide (BPO), *N*-hydroxyphthalimide (NHPI), and chiral NHC precursor **2a**[4] (Figure 1 and Table 1, entry 1). Although benzaldehyde failed to undergo amide formation, the reaction proceeded even at room temperature, and produced **3a** in 20% yield when triethylamine was replaced with diethylamine (entry 2). Without NHPI, the yield of **3a** decreased to 7% (entry 3).

These results led us to speculate that the pathway to amide **3a** was as follows (Scheme 1). First, aldehyde **1a** and diethylamine formed enamine, which was then oxidized by BPO to give α-benzoyloxy aldehyde **4**.[5] Diethylamine may have been produced by the reaction of triethylamine with BPO in entry 1.[6] The NHC underwent addition to **4** to form Breslow intermediate **5**. Liberation of benzoate followed by tautomerization gave acyltriazolium **6**,[2k] which was then converted into activat

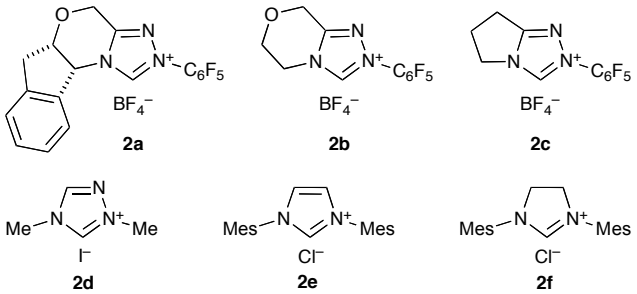
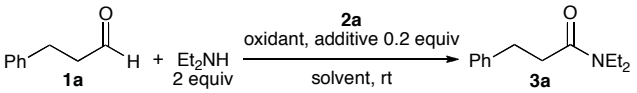


Figure 1. NHC Precursors **2a–f**

Table 1. Survey of Oxidant, Additive, and Catalyst Loading[a]



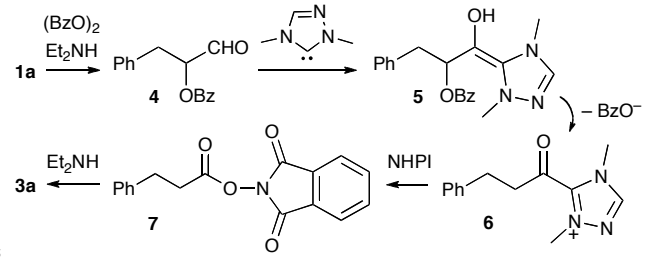
entry	oxidant/equiv	additive	**2a** mol %	time h	**3a** % yield
1[b]	$(BzO)_2$/0.6	NHPI	20	19	18
2	$(BzO)_2$/0.6	NHPI	20	20	20
3	$(BzO)_2$/0.6	-	20	17	7
4	$(BzO)_2$/1	NHPI	20	19	29
5	$(BzO)_2$/1	HOBt	20	18	45
6	$(BzO)_2$/2	HOBt	20	20	55
7	$(3\text{-}ClC_6H_4CO_2)_2$/2	HOBt	20	20	44
8	NIS/1.3	HOBt	20	10	20
9	NBS/1.3	HOBt	20	7	69
10	NCS/1.3	HOBt	20	6	76
11[c]	NCS/1.3	HOBt	20	6	96
12[c]	NCS/1.3	HOBt	10	12.5	92
13[c]	NCS/1.3	HOBt	5	12.5	88
14[c]	NCS/1.3	HOBt	2	12.5	79

[a] The solvent was toluene in entries 1–7 and CH_2Cl_2 in entries 8–14. [b] Under reflux with Et_3N instead of Et_2NH. [c] With 1.2 equiv Et_3N.

ed ester **7** by NHPI, and the diethylamine underwent acylation to produce amide **3a**. The failed reaction with non-enolizable benzaldehyde is also explained by this enamine-pathway.

Based on this hypothesized pathway, the reaction conditions were optimized. First, the reaction was performed with a stoichiometric amount of BPO, and **3a** was obtained in 29% yield after 19 h (entry 4). The use of 1-hydroxybenzotriazole (HOBt) instead of NHPI made the reaction cleaner, and gave **3a** in 45% yield (entry 5). Although other NHC precursors **2b–f** were tested, less satisfactory results were obtained.

Then, the reaction was performed with an increased amount of BPO (2 equiv), and the yield of **3a** slightly improved to 55% (entry 6). No improvement was observed when *m*-chlorobenzoyl peroxide was used in place of BPO, and **3a** was in 44% yield (entry 7). Then, NCS was tested as the oxidant, replacing BPOs. The reaction of **1a** with NCS (1.3 equiv) in dichloromethane produced **3a** in 76% yield (entry 10), though

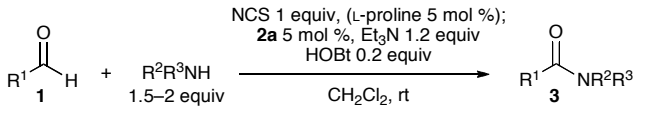


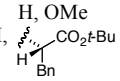
Scheme 1. Working Hypothesis

NIS and NBS gave less satisfactory results (entries 8 and 9). Finally, when the reaction was conducted with triethylamine (1.2 equiv) to neutralize the hydrogen chloride liberated during the reaction, **3a** was obtained in excellent yield after 6 h (entry 11). When the reaction was quenched after 30 min, **3a** was produced in 32% yield and α-chlorohydrocinnamaldehyde was mainly obtained in 60% yield. The chloroaldehyde and diethylamine were then converted into **3a** in 94% yield after 6 h in the presence of **2a** and triethylamine in dichloromethane at room temperature. These results indicate that the reaction proceed mainly through the α-chlorination of aldehyde followed by NHC-catalyzed acylation of nucleophiles, and not through oxidation of a Breslow intermediate. Thus, the reaction was best performed by pre-mixing **1a** and NCS in the presence of diethylamine before the addition of **2a**, triethylamine, and HOBt, and catalyst loading of **2a** was reducible (2–10 mol %) with only a slight decrease in the product yield (entries 12–14).

Other aldehydes and amines were applied to the reaction (Table 2). Linear aliphatic aldehyde **1b** was a good substrate, and amide **3b** was obtained in 91% yield (entry 2). A siloxy group was compatible with this transformation, and the reaction with aldehyde **1c** provided **3c** in 87% yield using 10 mol % **2a** (entry 3), though the yield was decreased to 56% with 5 mol % **2a**. α-Branched aldehyde was not suitable; the reaction of cyclohexanecarbaldehyde gave the corresponding diethylamide in only 25% yield. The reaction of **1a** and dibenzylamine gave *N*,*N*-dibenzyl amide **3d** in 49% yield along with *N*-benzyl amide **3e** in 11% yield. The production of **3e** indicates that dibenzylamine was debenzylated by the action of NCS. To avoid the reaction of the amine and NCS, an α-chlorination step was performed using L-proline as a catalyst; a solution of **2a**, triethylamine, HOBt, and dibenzylamine was added to a solution of **1a**, NCS, and L-proline (5 mol %) in dichloromethane pre-mixed for 9 h, and **3d** was obtained in 71% yield (entry 4). The use of L-proline was effective for the reactions of other amines. In the reaction of benzylamine, however, slow addition of the amine over 3 h was important to obtain **3e** in 72% yield (entry 5), and adding the amine in one portion decreased the yield to 39%. Formation of Weinreb amide efficiently proceeded, and the reaction of **1a** with methoxyamine hydrochloride salt provided **3f** in 81% yield (entry 6). An amino acid was also a good reaction partner; the reaction of **1a** and phenylalanine *tert*-butyl ester hydrochloride salt produced *N*-acyl amino acid **3g** without racemization (entry 7). The reaction rates of the amino acid enantiomers, however, were not significantly different, suggesting that amidation proceeded via an achiral intermediate such as **11** in Scheme 2.

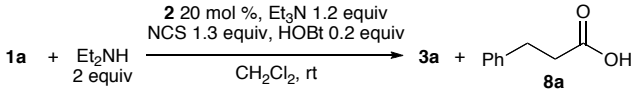
Table 2. NHC-Catalyzed Amidation of Aldehydes with Amines[a]



entry	**1**/R^1	amine[b] R^2, R^3	time/h	**3** % yield
1[c]	**1a**/Ph$(CH_2)_2$	Et, Et	12.5	**3a**/88
2	**1b**/Me$(CH_2)_5$	Et, Et	12	**3b**/91
3[d]	**1c**/TBSO$(CH_2)_3$	Et, Et	9	**3c**/87
4	**1a**/Ph$(CH_2)_2$	Bn, Bn	20	**3d**/71
5[e]	**1a**/Ph$(CH_2)_2$	H, Bn	23	**3e**/72
6[f]	**1a**/Ph$(CH_2)_2$	H, OMe	23	**3f**/81
7[f]	**1a**/Ph$(CH_2)_2$	H, 	19	**3g**/76[g]

[a] Entries 1–3 were conducted without L-proline, while entries 4–7 were conducted with L-proline. [b] Used 2 equiv in entries 1–3 and 1.5 equiv in entries 4–7. [c] From Table 1, entry 13 for comparison. [d] With 10 mol % **2a**. [e] $BnNH_2$ was added over 3 h. [f] HCl salt of R^2R^3NH was added instead of free amine. [g] Without racemization.

Table 3. NHC-Dependent Selectivity between Formation of **3a** and **8a**.

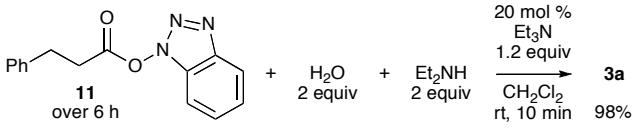


entry	**2**	time/h	**3a**/% yield	**8a**/% yield
1[a]	**2a**	6	96	0
2	**2b**	6	67	14
3	**2c**	6	23–37[b]	31–38[b]
4[c]	**2a**	7	90	6
5[c]	**2c**	6	10	83

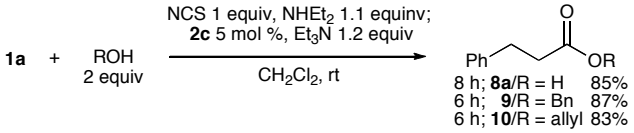
[a] From Table 1, entry 11 for comparison. [b] Range of three reactions. [c] In the presence of 2 equiv H_2O.

Studies to investigate the best NHC catalyst under the conditions using NCS revealed that **2a** was the best among **2a**–**f**, and also led to an interesting NHC-dependent selectivity switching of the nucleophilic partner. When the reaction was conducted in the presence of triazolium **2b**, instead of **2a**, along with amide **3a** in 67% yield, carboxylic acid **8a** was obtained in 14% yield (Table 3, entry 2). With triazolium **2c**, **8a** and **3a** were obtained in similar amounts (31–38% and 23–37%, respectively) (entry 3), while complex mixtures were produced using **2d**–**f**. The varying yields of **3a** and **8a** in the reaction with **2c** indicate that the formation of the carboxylic acid is due to a reaction of intermediate **6** or **7** with exogenous water. Indeed, additional water (2 equiv) increased the yield of the carboxylic acid, and we obtained **8a** in 83% yield and **3a** in 10% yield (entry 5). In contrast, the reaction with NHC derived from **2a** preferentially produced amide **3a** even in the presence of water (entry 4).

In this reaction, amides were likely formed via activated esters **11**, because acylazoliums, such as **6**, react predominantly with water and alcohols over amines,[7] and indeed, the yield of amide **3a** was poor without NHPI and HOBt (Table 1, entry 3). Recently, activation of O-nucleophiles by hydrogen bonding with NHC was proposed to explain the O-preference of acylazoliums;[3e,8] thus, a competitive reaction of water and diethylamine with benzotriazolyl ester **11** was conducted in the presence of 20 mol % **2c** (Scheme 2). Although **11** was slowly added over 6 h, no activation of water over amine was observed, and amide **3a** was quantitatively produced. This



Scheme 2. Reaction of Benzotriazolyl Ester **11** with Diethylamine in the Presence of Water and **2c**-derived NHC.



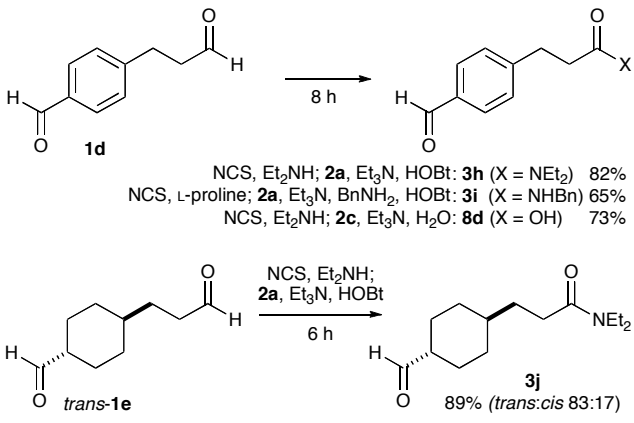
Scheme 3. Reaction of **1a** with O-Nucleophiles.

result also indicates that carboxylic acid **8a** was directly produced by the reaction of acyltriazolium **6** with water.

As expected from the pKa values (HOBt 4.6,[9] water 15.7), DFT calculations suggested higher stability of an NHC–HOBt hydrogen-bond complex, in which the O–H bond of HOBt was more elongated and thus activated, than an NHC–water complex.[10] The reaction of HOBt was, however, faster than that of water with more bulky **2a**-derived NHC (entry 4), and became slower with less bulky **2c**-derived NHC (entry 5). In contrast to entry 5, using 5 mol % **2c**, **3a** was produced in 43% yield with **8a** in 53% yield. These results are contradictory to the hydrogen-bond activation model, and seem to suggest that a hydrogen bond with NHC is not an important factor of the chemoselectivity of acylazoliums, at least in this reaction, although the choice of the NHC catalyst controls whether acyltriazolium **6** reacts with HOBt or water.

Thus, the reaction of O-nucleophiles was best performed with 1.1 equiv of diethylamine in the absence of HOBt. In the presence of 5 mol % **2c**, carboxylic acid **8a** was obtained in 85% yield without production of amide **3a** (Scheme 3). Alcohols such as benzyl and allyl alcohols were also good nucleophiles, and aldehyde **1a** was converted into the corresponding esters **9** and **10**, respectively, in good yields.

Taking advantage of this reaction, chemoselective conversion of dialdehyde **1d** and **1e** was demonstrated (Scheme 4). With **1d** having both aliphatic and aromatic formyl groups, the reaction with diethylamine and water gave amide **3h** in 82% yield and carboxylic acid **8d** in 73% yield. The reaction of benzylamine also proceeded in a chemoselective manner using proline as a co-catalyst to give α-unbranched amide **3i** in 65% yield and no amidation of the aromatic aldehyde moiety was observed. The reaction of diethylamine and **1e** having both α-branched and α-unbranched aldehyde moieties proceeded selectively at the α-unbranched moiety to provide mono-amide **3j** in 89% yield. Partial isomerization (*trans* only to *trans*:*cis* 83:17) was observed at the α-position of the branched aldehyde moiety in the reaction of **1e**, suggesting reversible enamine formation of the α-branched aldehyde moiety. Therefore, the selectivity is likely due to the slower chlorination of the more hindered enamine.



Scheme 4. Chemoselective Conversion of α-Unbranched Aldehyde to Amide and Carboxylic Acid

In summary, we developed a new one-pot transformation of α-unbranched aldehydes to amide, ester, and carboxylic acid with NHC-catalysis. It is advantageous that selective conversion of α-unbranched aldehydes is possible and isolation of unstable α-chloroaldehyde intermediates is unnecessary. The observed NHC-dependent nucleophile-selectivity shows that chemoselectivity can be controlled by the selection of the NHC-catalyst.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, characterization data and NMR charts of products, HPLC traces of **3g**, and results of DFT calculations. See DOI: 10.1039/b000000x/

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